REMARKS

I. Status of the Claims

Claims 1, 3-6 and 8-13 are pending in the application, and claims 1, 6, 8, 9 and 11-13 stand withdrawn. Thus, claims 3-5 and 10 are under consideration and stand rejected under either 35 U.S.C. §102 or 35 U.S.C. §103. The specific grounds for rejection, and applicant's response thereto, are set out in detail below.

II. Amendments and Alleged Constructive Election

Claim 4, the only independent claim under consideration, has been amended to employ use of the transitional phrase "consisting of," and thus now recites that Annexin V or a salt thereof, or a dimer and/or a PEG conjugate of Annexin V or salt thereof, is the only active component in the pharmaceutical composition.

The examiner argues that the alternative claim recitations of Annexin V dimers and PEG conjugates are patentably distinct embodiments, and thus applicant's earlier prosecution of Annexin V is a constructive election allowing these alternative species to be withdrawn.

Without commenting on the patentably distinct nature of these species, applicant traverses the examiner's statement that the species "do not share a common structure that is disclosed to be essential for common utility." Indeed, these species have an ***identical*** common structure, namely, Annexin V. In one case there are simply two Annexin V molecules, and in the other, the Annexin V is merely PEG-conjugated. Thus, there is unquestionably a common structure. There is no specific assertion by the action, nor any basis to believe, that the mechanism of action (in the context of claim 4) would differ either.

The treatment of Markush-type claims in the context of restriction/election is governed by MPEP §803.02. This section states that "when the Markush group occurs in a claim reciting a process or a combination (not a single compound), it is sufficient if the members of the group are disclosed in the specification ***to possess at least one property in common which is mainly responsible for their function in the claimed relationship, and it is clear from their very nature or from the prior art that all of them possess this property***" (emphasis added). Indeed, it further states that "If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions." The examiner is instructed that, in such a case, the provisional election of a single species for prosecution is ***not*** required.

This section further cites to decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), as support for the rule that it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). More specifically, unity of invention is defined as existing where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature essential to that utility. There simply is no reasonable basis for concluding, in this case, that the alternative species lack, with the respect to Annexin V, either a common utility or common structural features essential to that utility.

Furthermore, once the examiner determines that Annexin V is allowable, the examination of the Markush-type genus must be extended. Only if prior art is then found that anticipates or

renders obvious the Markush-type claim with respect to the rejoinded species will the Markush-type claim be rejected and claims to the nonelected species held withdrawn from further consideration.

In light of these rules, applicant submits that there should be no election under these circumstances, but if there is, rejoinder of the alternative species is required upon the allowability of Annexin V.

III. Rejection Under 35 U.S.C. §102

Claims 4 and 10 are rejected as anticipated by Blankenberg. As explained in detail below, applicants once again traverse.

The examiner argues that paragraph [0011] Blankenberg reports that Annexin V itself has anti-apoptotic activity (and other effects, including inhibition of membrane permeability to calcium, protein kinase C and phospholipase A2 *in vitro*). Thus, it is alleged that the reference taught the use of Annexin V alone to prevent plaque rupture. However, this allegation overlooks the following:

(a) Paragraph [0011] of Blankenberg merely discloses that unlabelled Annexin V has anti-apoptotic activity (and other effects, including inhibition of membrane permeability to calcium, protein kinase C and phospholipase A2 *in vitro*). This is not a disclosure of the use of unlabelled Annexin V to prevent plaque rupture. Blankenberg makes no suggestion that an anti-apoptotic effect (or any of the other effects attributed to Annexin V in Blankenberg) would be useful in the context of preventing plaque rupture.

(b) The only specific disclosure in Blankenberg of the treatment of vulnerable atherosclerotic plaques is in respect of the use a complex of Annexin V, a radioisotope and an effector molecule to selectively kill or inactivate apoptotic cells in an atherosclerotic plaque. See Blankenberg, paragraph [0032], which states its complexes can be used for "treating vulnerable plaques" via the activity of the effector molecule portion of the complex which "will selectively kill or inhibit the stressed or apoptotic cells associated with the vulnerable plaque."

Moreover, it is not possible to derive from Blankenberg that the ***anti***-apoptotic effect provided by Annexin V could be therapeutically beneficial in the prevention of plaque rupture. On the contrary, paragraph [0032] of Blankenberg teaches that its complexes can be used for "treating vulnerable plaques" via the activity of the effector molecule portion of the complex which "will selectively kill or inhibit the stressed or apoptotic cells associated with the vulnerable plaque." Thus, selective killing or inactivation of cells in an atherosclerotic plaque – clearly the teaching of Blankenberg – is clearly the direct opposite of preserving such cells by ***preventing*** apoptosis.

The entire focus of Blankenberg is that, in order to treat vulnerable plaques, one should selectively kill cells therein using the disclosed complex. The disclosure relied on by the examiner in paragraph [0011] of Blankenberg clearly cannot be taken as a teaching of using unlabelled Annexin V to prevent the rupture of atherosclerotic plaques. Accordingly, the reader of Blankenberg is given no reason to understand that Annexin V alone, and the anti-apoptotic effect that is attributed to it, should be used to prevent plaque rupture. In fact, Blankenberg teaches something quite different, since it instructs that plaque rupture should be prevented by the ***selective killing of plaque cells***, rather than preserving the life of the plaque cells by preventing apoptosis. Accordingly, in light of the teaching of Blankenberg, the skilled person

would not have understood that plaque rupture was to be treated using Annexin V alone. Much to the contrary, they would actually have expected the reported anti-apoptotic effect of Annexin V to have the ***reverse*** effect and ***promote*** plaque rupture. This is consistent with the understanding in the art of the mechanism of plaque rupture, as further supported by Merched *et al.*, 2003, *Arterioscler. Thromb. Vasc. Biol.*, 23, 1608-1614 (listed in IDS submitted to USPTO with letter of August 2, 2007). This document reports that:

- macrophages are the major cellular components of atherosclerotic plaques and they undergo both proliferation and apoptosis, processes tightly regulated by the tumor suppressor protein p53 (see page 1608, left-hand column, first paragraph);
- macrophage proliferation in atherosclerotic lesions (plaques) occurs more readily in the absence of p53 expression (page 1611, left-hand column, line 6 *et seq*); and
- p53 expression confers stability to plaques, whereas the absence of p53 expression renders plaques more vulnerable to rupture (page 1612, paragraph bridging left and right columns, particularly the final two sentences).

Therefore, Merched *et al.* shows that an absence of p53 expression correlates both with high macrophage proliferation and with increased risk of plaque rupture. In other words, according to the teaching of Merched *et al.*, increased macrophage proliferation appears to be related to an increased risk of plaque rupture. Increased macrophage proliferation would be expected to be the result of the prevention of macrophage apoptosis. Annexin V is taught by Blankenberg to provide an anti-apoptotic effect generally. Therefore, it follows that, in light of Merched *et al.*, one of skill in the art would have expected that the anti-apoptotic effect of Annexin V taught by Blankenberg on plaques would be increase in macrophage proliferation and, thus, an increased risk of rupture. This is directly opposite to the present invention.

Further evidence that anti-apoptotic effects would not have been expected in the art as being useful to prevent plaque rupture can be taken from reports that statins (HMG-CoA reductase inhibitors) induce apoptosis but reduce plaque instability, i.e. promote plaque stability. For example (by reference to the following documents that were all listed in IDS filed on January 25, 2010):

- evidence that statins were known in the art to induce apoptosis can be taken from Kaneta *et al.*, 2003, *Athersclerosis*, 170, 237-243 and Blanco-Colio *et al.*, 2002, *Atherosclerosis*, 161, 17-26 (see titles of each report); and
- evidence that statins were known in the art to reduce plaque instability can be taken from Gomberg-Maitland *et al.*, 2003, *J. Cardiovasc. Risk*, 10, 161-167 (see page 164, right-hand column, 2nd paragraph "Statins stabilize plaques at the cellular and molecular level.").

In view of these reports, the understanding is that statins promote apoptosis and stabilize plaques, and so one of skill in the art would not have expected any agent known to inhibit apoptosis (such as Annexin V, as taught by Blankenberg) to contribute to plaque stability.

Thus, there was clearly no understanding or expectation in the art that apoptosis had any role in plaque stability at all and, to the extent that there was any established view, the weight of direct evidence was that inhibition of apoptosis would likely result in increased risk of plaque rupture. Accordingly, given that Blankenberg teaches that Annexin V has the ability to inhibit apoptosis, it must be understood to further teach that it is useful only as a complex with another agent. The skilled person would not have understood this reference to use Annexin V alone to treat or prevent plaque rupture, and indeed, would have been surprised that plaque rupture could be prevented using Annexin V alone in accordance with the present invention.

Because the presently amended claims exclude the use of Annexin V as a complex with another active agent, and because Blankenberg clearly provide ***only*** Annexin V therapeutic ***complexes***, the reference cannot be anticipatory. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Rejection Under 35 U.S.C. §103

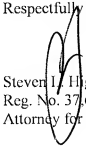
Claims 3-5 are rejected as obvious over Blankenberg in view of Manzi *et al.* Applicants traverse.

Once again, as explained in detail above, Blankenberg does not teach or suggest that Annexin V could be used as a single agent to prevent plaque rupture (as now required in the claims), and Manzi does not correct this deficiency. Indeed, Manzi says nothing about Annexin V or its uses, and further says nothing about a possible role for apoptosis in plaque rupture. Thus, it too fails to motivate the skilled person to use Annexin V alone to prevent plaque rupture. Accordingly, even if the skilled person were to have combined Blankenberg and Manzi, their combined teachings still could not render the present invention obvious. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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Date: May 23, 2011